The phosphodiesterases type 5 inhibitor tadalafil reduces the activation of the hypothalamus-pituitary-adrenal axis in men during cycle ergometric exercise

**Luigi Di Luigi,1 Paolo Sgrò,1 Carlo Baldari,2 Maria Chiara Gallotta,2 Gian Pietro Emerenziani,2 Clara Crescioli,1 Serena Bianchini,1 Francesco Romanelli,3 Andrea Lenzi,3 and Laura Guidetti2**

1Unit of Endocrinology and 2Unit of Sport and Exercise Sciences, Department of Health Sciences, University of Rome “Foro Italico,” Rome; and 3Department of Experimental Medicine, University of Rome “Sapienza,” Rome, Italy

Address for reprint requests and other correspondence: L. Di Luigi, Unit of Endocrinology, Dept. of Health Sciences, Univ. of Rome “Foro Italico,” Piazza Lauro de Bosis, 15, 00135 Rome, Italy (e-mail: luigi.diluigi@uniroma4.it).

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First published February 7, 2012; doi:10.1152/ajpendo.00573.2011.—Phosphodiesterase type 5 inhibitors may influence human physiology, health, and performance by also modulating endocrine pathways. We evaluated the effects of a 2-day tadalafil administration on adrenohypophysal and adrenal hormone adaptation to exercise in humans. Fourteen healthy males were included in a double-blind crossover trial. Each volunteer randomly received two tablets of placebo or tadalafil (20 mg/day with a 36-h interval) before a maximal exercise was performed. After a 2-wk washout, the volunteers were crossed over. Blood samples were collected at −30 and −15 min and immediately before exercise, immediately after, and during recovery (+15, +30, +60, and +90 min) for adrenocorticotropic (ACTH), β-endorphin, growth hormone (GH), prolactin, cortisol (C), corticosterone, dehydroepiandrosterone-sulfate (DHEAS), and cortisol binding globulin (CBG) assays. C-to-CBG (free cortisol index, FCI) and DHEAS-to-C ratios were calculated. Exercise intensity, perceived exertion rate, O2 consumption, and CO2 and blood lactate concentrations were evaluated. ACTH, GH, C, corticosterone, and CBG absolute concentrations and/or areas under the curve (AUC) increased after exercise after both placebo and tadalafil. Exercise increased DHEAS only after placebo. Compared with placebo, tadalafil administration reduced the ACTH, C, corticosterone, and FCI responses to exercise and was associated with higher β-endorphin AUC and DHEAS-to-C ratio during recovery, without influencing cardiorespiratory and performance parameters. Tadalafil reduced the activation of the hypothalamus-pituitary-adrenal axis during exercise by probably influencing the brain’s nitric oxide- and cGMP-mediated pathways. Further studies are necessary to confirm our results and to identify the involved mechanisms, possible health risks, and potential clinical uses.

nitric oxide; exercise; tadalafil; adrenocorticotropic; cortisol

THE SECRETION OF SYSTEMIC stress mediators (e.g., catecholamines, pituitary and adrenal hormones) increases after exercise depending on type, intensity, and duration of performed physical activity, individual characteristics, and associated psychological and metabolic stressors (7, 17, 21, 29, 36, 48). In addition, many prohibited (e.g., anabolic hormones, glucocorticoids) and nonprohibited [e.g., nonsteroidal anti-inflammatory drugs, phosphodiesterases type 5 (PDE5) inhibitors (PDE5i), amino acids] substances, largely used or abused by athletes, have been shown to influence exercise performances and/or endocrine pathways at rest and during exercise (9–11, 13, 19, 22).

The PDE5i (e.g., sildenafil, tadalafil) widely used to treat erectile dysfunction in males have been shown to differently influence exercise capacity and/or energy metabolism during exercise, both in subjects affected by cardiopulmonary diseases and in healthy individuals, depending on the type and doses of PDE5i, oxygen availability, and exercise characteristics (1, 10, 15, 18, 23). On these bases, PDE5i are suggested as therapy to improve exercise capacity in individuals affected by cardiopulmonary diseases, and, from anecdotal reports, they are largely abused by healthy athletes to fraudulently enhance sport performance.

Even if cardiovascular mechanisms probably predominate (28), at least in theory, PDE5i use, or abuse, could affect health and/or exercise performance by also influencing endocrine and/or metabolic pathways. In fact, it is known that: 1) PDE5i block the degradative action of PDE5 on the intracellular cGMP, 2) cGMP is one of the intracellular transduction mediators of nitric oxide (NO), and, 3) NO may influence both energy substrate metabolism and pituitary/adrenal hormone secretion by cGMP-dependent -independent (e.g., Ca2+, prostaglandins) mechanisms (14, 25–27, 33, 34, 42, 45, 54). Therefore, PDE5 inhibition may enhance the cGMP-dependent endocrine/metabolic effects of NO by further increasing and/or maintaining the intracellular levels of NO-induced cGMP.

Unfortunately, few studies reported endocrine/metabolic effects of PDE5i during the physiological adaptation to standardized exercises in healthy individuals. Particularly, in two exploratory studies, we showed that, in healthy males, a brief exposure to the long-acting PDE5i tadalafil (i.e., 20 mg administered 8 h before exercise) increased salivary cortisol after maximal aerobic exercise (11) and blood lactate after anaerobic power exercise (18), without influencing physical performance. Interestingly, tadalafil has been shown to modulate energy metabolisms in C2C12 skeletal muscle cells in vitro depending on its doses and duration of exposure (47).

On this basis, and because hormone activation during exercise is related to metabolic stress (7), it is possible that the effects of tadalafil on endocrine adaptation during exercise are also related to the doses/duration of administration. In this sense, we aimed to evaluate if a prolonged exposure to tadalafil, with respect to our previous study design (11), could differently affect adrenal cortex activation and exercise performance during maximal exercise in healthy humans. In addition, we also aimed to evaluate whether tadalafil could affect the
activation of pituitary hormones during exercise. To this end, we
analyzed the effects of two consecutive days of tadalafil
administration on performance parameters and on adeno-
hypophyseal and adrenal cortex stress hormone responses
to exhaustive exercise in men in a double-blind crossover
experimental design.

RESEARCH DESIGN AND METHODS

Subjects. For inclusion, a group of students of our University
underwent: 1) an endocrinological and sexual history and physical
examination conducted by an endocrinologist and 2) a prepartici-
aption screening [history, physical examination, 12-lead electrocar-
diogram (ECG), spirometry] conducted by a sport physician. Exclusion
criteria were: 1) an abnormal physical development and functions,
2) the presence of symptoms and/or positive history for endocrine,
cardiovascular, pulmonary, retinal, sexual, and psychiatric diseases,
3) the use of drugs or supplements, and 4) the presence of major stress
events, contraindicating and/or interfering with the experimental eval-
uations. Fourteen healthy nonsmoking trained male volunteers, in-
volved in noncompetitive team sports, were included. University Ethical
Committee approval and written informed consent were ob-
tained. Weight was measured on a digital scale with an accuracy of
0.1 kg, after the removal of shoes and heavy clothing (only underwear
on). A Harpenden’s stadiometer (St. Albans, UK) was used for height
measurement. Body mass index (BMI) was determined by dividing
the weight by the square of the height (kg/m²). One week before
starting the experimental phase, each volunteer underwent a maximal
exercise test, to get familiarized with the protocol and to evaluate the
maximal oxygen uptake (VO2max) by using an electronic cycle-
ergometer (Excalibur Lode, Groningen, The Netherlands) and an
open-circuit spirometry system (Quark b²; COSMED, Rome, Italy), as
previously described (25). The volunteer’s characteristics were
[means ± SD (min-max)]: age 26 ± 3.6 (19–31) yr, height 172.2 ±
7.0 (157.0–184.0) cm, weight 71.3 ± 5.9 (65.0–84.0) kg, BMI
24.0 ± 2.0 (21.9–28.4) kg/m², VO2max 48.7 ± 5.1 (40.1–56.0)
mL/min·kg⁻¹.

Experimental protocol and laboratory procedures. In the double-
blind experimental phase, all volunteers performed an exercise test to
exhaustion on a cycle ergometer, after randomly receiving two tablets
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mL/min·kg⁻¹.
respectively; \(P = \text{NS}\), and systolic blood pressure (123.3 ± 8.7 and 122.8 ± 7.9 mmHg, respectively; \(P = \text{NS}\)) were observed.

Exercise characteristics and physiological adaptive parameters during exercise were similar after placebo and tadalafil administration (Table 1). No variations in hematocrit were found at any time points (data not shown). Hormonal results are reported in Tables 2 and 3 and in Fig. 1. No effects of tadalafil on preexercise hormone concentrations and AUCs were observed.

**ACTH.** ACTH concentration increased after exercise, from 0-post to +15 min of recovery, following both placebo and tadalafil (Fig. 1A). Compared with placebo, ACTH concentration was lower after tadalafil at 0-post (from 8.4 to 0.9, \(P = 0.05\)) and +30 min after tadalafil (Fig. 1B). Compared with placebo, ACTH concentration was lower after tadalafil at +15, +30, +60, and +90 min of recovery (from 26.3, 23.2%, and 22.6%, respectively), with no differences between placebo and tadalafil at 0.0001). Compared with placebo, ACTH concentration was lower after tadalafil (Fig. 1B). Mean preexercise CBG concentration increased immediately after exercise after both placebo (from 23.2 to 56.7 mg/l, \(P = 0.001\)) and tadalafil (from 23.2 to 59.8 mg/l, \(P < 0.0001\), and no differences between placebo and tadalafil were observed before and after exercise (\(P = 0.157\) and 0.109, respectively). Mean preexercise FCI increased immediately after exercise, after both placebo (from 8.9 to 12.1, \(P < 0.0001\)) and tadalafil (from 8.2 to 10.5, \(P < 0.0001\)). Compared with placebo, FCI after exercise was lower after tadalafil administration (\(P = 0.016\)).

**Corticosterone.** Corticosterone concentration increased immediately after exercise after both placebo and tadalafil (Fig. 1C). During recovery, corticosterone concentration remained higher than preexercise values at +15 and +30 min after placebo and at +15 min after tadalafil (Fig. 1C). Compared with placebo, corticosterone concentration was significantly lower after tadalafil at +15 min and +30 min (at 0.001 and \(P = 0.0001\), respectively). Corticosterone levels were significantly lower after tadalafil administration at +30 min (at 0.01 and **0.001**, respectively) (Fig. 1C).

Table 1. Exercise and physiological characteristics

<table>
<thead>
<tr>
<th>Exercise characteristic</th>
<th>Placebo</th>
<th>Tadalafil</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration, min</td>
<td>22.3 ± 2.4</td>
<td>21.7 ± 1.6</td>
<td>0.245</td>
</tr>
<tr>
<td>Ratings of perceived exertion*</td>
<td>18.5 ± 0.9</td>
<td>18.6 ± 1.0</td>
<td>0.435</td>
</tr>
<tr>
<td>Maximum exercise intensity, watts</td>
<td>275.0 ± 25.0</td>
<td>282.5 ± 27.0</td>
<td>0.245</td>
</tr>
<tr>
<td>(V_{O_{2peak}}), ml/min</td>
<td>3462.7 ± 338.9</td>
<td>3314 ± 280.2</td>
<td>0.129</td>
</tr>
<tr>
<td>Respiratory exchange rate* ((VCO_{2}/V_{O_{2}}))</td>
<td>1.09 ± 0.08</td>
<td>1.15 ± 0.06</td>
<td>0.061</td>
</tr>
<tr>
<td>Maximum lactate concentration, mmol/l</td>
<td>10.9 ± 2.6</td>
<td>10.7 ± 1.7</td>
<td>0.806</td>
</tr>
<tr>
<td>Maximum heart rate, beats/min</td>
<td>183.8 ± 8.2</td>
<td>185.4 ± 10.8</td>
<td>0.428</td>
</tr>
<tr>
<td>Diastolic blood pressure*, mmHg</td>
<td>83.5 ± 6.9</td>
<td>81.2 ± 7.1</td>
<td>0.425</td>
</tr>
<tr>
<td>Systolic blood pressure*, mmHg</td>
<td>181.7 ± 2.6</td>
<td>180.1 ± 10.4</td>
<td>0.796</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. The parameters are evaluated during an acute maximal exercise test on a cycle ergometer, both after placebo and tadalafil administration, in healthy male volunteers (\(n = 14\)). *At the end of exercise.

**Table 2. Serum hormone concentrations and ratios at rest and after exercise**

<table>
<thead>
<tr>
<th></th>
<th>-30</th>
<th>-15</th>
<th>0-Pre</th>
<th>0-Post</th>
<th>+15</th>
<th>+30</th>
<th>+60</th>
<th>+90</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta)-Endorphin, pg/ml</td>
<td>41.3 ± 32.6</td>
<td>48.7 ± 28.6</td>
<td>47.7 ± 33.2</td>
<td>36.6 ± 24.9</td>
<td>38.7 ± 32.1</td>
<td>44.2 ± 36.6</td>
<td>38.3 ± 33.8</td>
<td>38.6 ± 38.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>44.9 ± 28.4</td>
<td>47.1 ± 33.0</td>
<td>46.1 ± 26.1</td>
<td>51.6 ± 28.9</td>
<td>49.6 ± 28.6</td>
<td>52.4 ± 47.6</td>
<td>50.6 ± 32.7</td>
<td>50.7 ± 31.9</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>0.36 ± 0.13</td>
<td>0.42 ± 0.43</td>
<td>0.31 ± 0.07</td>
<td>26.1 ± 19.8**</td>
<td>21.7 ± 16.5**</td>
<td>11.1 ± 10.5**</td>
<td>2.5 ± 2.7**</td>
<td>1.08 ± 1.0*</td>
</tr>
<tr>
<td>GH, mIU/l</td>
<td>0.31 ± 0.08</td>
<td>0.30 ± 0.06</td>
<td>0.36 ± 0.11</td>
<td>20.4 ± 21.5**</td>
<td>18.4 ± 17.9**</td>
<td>11.3 ± 10.8**</td>
<td>2.9 ± 3.0*</td>
<td>1.3 ± 1.2*</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.4 ± 7.1</td>
<td>11.8 ± 7.2</td>
<td>11.1 ± 6.5</td>
<td>11.8 ± 7.0</td>
<td>10.7 ± 5.9</td>
<td>9.2 ± 4.4</td>
<td>7.6 ± 3.7</td>
<td>6.4 ± 3.1*</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>11.9 ± 5.8</td>
<td>11.2 ± 5.4</td>
<td>12.1 ± 9.5</td>
<td>9.3 ± 4.8</td>
<td>8.7 ± 4.3</td>
<td>8.9 ± 5.7</td>
<td>7.3 ± 3.8</td>
<td>6.4 ± 3.5*</td>
</tr>
<tr>
<td>PRL, ng/ml</td>
<td>Placebo</td>
<td>329.8 ± 133.8</td>
<td>324.8 ± 139.3</td>
<td>313.3 ± 119.7</td>
<td>369.4 ± 146.6**</td>
<td>355.0 ± 114.4*</td>
<td>352.6 ± 124.6*</td>
<td>349.2 ± 132.6**</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>352.0 ± 152.8</td>
<td>351.2 ± 147.9</td>
<td>357.4 ± 170.1</td>
<td>374.2 ± 160.2</td>
<td>355.9 ± 138.3</td>
<td>339.1 ± 134.4</td>
<td>331.6 ± 151.2</td>
<td>365.7 ± 177.0</td>
</tr>
<tr>
<td>DHEAS, µg/100 ml</td>
<td>Placebo</td>
<td>0.66 ± 0.33</td>
<td>0.73 ± 0.39</td>
<td>0.79 ± 0.41</td>
<td>0.59 ± 0.27*</td>
<td>0.57 ± 0.25*</td>
<td>0.63 ± 0.29</td>
<td>0.76 ± 0.37</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>0.81 ± 0.54</td>
<td>0.85 ± 0.43</td>
<td>0.93 ± 0.56</td>
<td>0.75 ± 0.42</td>
<td>0.75 ± 0.35#</td>
<td>0.83 ± 0.39#</td>
<td>1.07 ± 0.61#</td>
<td>1.26 ± 0.78#</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. GH, growth hormone; PRL, prolactin; DHEAS, dehydroepiandrosterone-sulfate; C, cortisol. The parameters are evaluated 30 and 15 min (−30, −15) and immediately before (0-pre) starting an acute maximal exercise test on a cycle ergometer, at the end of exercise (0-post), and at +15, +30, +60, and +90 min of recovery, both after placebo and tadalafil administration, in healthy male volunteers (\(n = 14\)). *\(P < 0.05\) and **\(P < 0.01\) vs. respective 0-pre. #\(P < 0.05\) vs. respective placebo.
lower after tadalafil at +15, +30, and +60 min of recovery (−32.2, −37.3, and −37.0%, respectively) (Fig. 1C). Corticosterone-post.exAUC was higher than respective pre.exAUC only after placebo (Table 3). Compared with placebo, corticosterone-post.exAUC was lower after tadalafil (Table 3).

**DHEAS-to-C ratio.** The DHEAS-to-C ratio after exercise decreased after placebo, from 0-post to +15 min of recovery, and increased after tadalafil at +90 min of recovery (Table 2). Compared with placebo, the DHEAS-to-C ratio was higher after tadalafil from +15 to +90 min of recovery (Table 2).

**DISCUSSION**

Besides the physiological variability in individual hormone concentrations and responsiveness to exercise, we showed for the first time that a 48-h systemic exposure to tadalafil reduced the physiological hypothalamus-pituitary-adrenal (HPA) axis activation during a standardized maximal exercise in healthy men, without modifying cardiorespiratory parameters and physical performance. Otherwise, the exercise-related GH increase was not influenced by tadalafil administration. Moreover, because in a different study design the postexercise salivary C increased after a brief exposure to tadalafil (11), our results confirm that tadalafil may differently affect the HPA axis activation during exercise depending on the characteristics of administration.

This study design was not addressed to identify either the pathways whereby tadalafil interacts with hormones during exercise or the fine mechanisms by which different tadalafil treatments could differently affect the HPA axis. Consequently, we could only make hypotheses on the pathways involved in the observed effects of tadalafil on the HPA axis during exercise and speculate on possible consequences/applications of our results.

**Tadalafil and ACTH response to exercise.** Whenever exercise activates the HPA axis (7, 27, 29, 39, 53), the neurons of paraventricular nuclei (PVN) in the hypothalamus secrete corticotrophin-releasing hormone (CRH) that stimulates pituitary ACTH, that in turn stimulates adrenal steroid output.

Because of the absence of modifications in metabolic parameters between the placebo and tadalafil group (e.g., lactate production, $O_2$ consumption), we hypothesize that tadalafil, after crossing the blood-brain barrier (49, 55), first reduced the ACTH activation by influencing NO-mediated pathways (see Introduction) in the central nervous system (CNS). Probably, tadalafil affected ACTH secretion by inhibiting the PDE5 expressed in CNS (32), thus enhancing cGMP-mediated effects of NO on the hypothalamus-pituitary axis. In fact, NO-producing neurons are densely localized in PVN, and NO modulates the HPA axis by acting on different neuroendocrine pathways (5, 14, 24, 30, 33, 45, 46). Our hypothesis is supported by data from animals showing that: 1) NO exerts a tonic negative influence on the HPA axis (16), 2) NO may differently influence (e.g., increase or decrease) the activation of PVN during stress (24, 27, 51), and 3) in Yucatan swine, the inhibition of NO synthase increased the ACTH response to exercise (24).

The involvement of NO- and cGMP-mediated effects of tadalafil in CNS is further suggested by the fact that, in our study, the GH activation was not affected by tadalafil; in fact, NO has been reported to modulate GH secretion by influencing cGMP-independent pathways (42).

In this context, it is difficult to establish whether the higher mean postexercise β-endorphin AUC after tadalafil, with respect to placebo, is related to tadalafil or to individual variability. In fact, NO may induce both a neuronal release of...
Tadalafil, HPA axis, and body’s adaptation to exercise. The activation of the HPA axis during exercise plays a pivotal health-protective and adaptive role by influencing mood status, cognitive processes, the cardiovascular system, fuel metabolism, and fluid homeostasis (42, 50, 53). Unfortunately, adrenal glucocorticoids are also responsible for stress-related diseases, altered anabolic/catabolic status, adrenal hyperplasia and hypertrophy, and overtraining and reproductive dysfunctions, both in humans and in animals (4, 6, 20, 35, 40, 52).

In our study, despite a reduced C and corticosterone secretion after tadalafil administration, neither serious adverse events nor modifications of physiological parameters/perceived exertion during exercise were observed. Consequently, in the actual experimental conditions, we could speculate on a possible positive anti-stress-like effect of tadalafil during exercise because of reduced glucocorticoid-related risks and exercise capacity maintenance. Moreover, because C is a catabolic hormone for proteins, the effect of suppressing C during exercise may have a beneficial training effect because tadalafil might enhance training-induced protein accretion in muscles (e.g., if confirmed, may be a doping effect in athletes). When an anti-stress-like effect of tadalafil is suggested, we also highlight that, compared with placebo, the DHEAS-to-C ratio during recovery was higher after tadalafil. In fact, the DHEAS-to-C ratio may influence the anabolic/catabolic balance, is negatively correlated with training load in athletes, and is an index of the degree of which an individual is buffered against stress-related damages, since higher DHEAS-to-C ratios are associated with a better health-protective capacity (4, 12, 38, 40). Besides the reported theoretical positive effects of tadalafil during exercise, due to some limitations of actual investigation (e.g., reduced set of measurements, lack of data in different experimental conditions), we cannot exclude that in particular situations (e.g., prolonged exercises, severe environmental conditions, etc.) health status and/or exercise performance could be negatively affected by a tadalafil-related HPA axis inhibition.

In conclusion, a 2-day tadalafil administration reduced the HPA axis activation during maximal exercise in healthy men by probably acting on NO- and cGMP-mediated pathways in the CNS and without influencing the main performance and cardiorespiratory parameters. Despite actual results, and although already hypothesized for cardiovascular diseases (26), it is premature to speculate on a possible preventive or therapeutic role for tadalafil also in stress-related diseases/conditions (e.g., depression, metabolic syndrome, sexual and reproductive dysfunctions, overtraining). Further studies are warranted to verify our results in different experimental conditions (e.g., for number of subjects, race, gender, fitness status, type of stressor) and to evaluate all possible mechanisms whereby tadalafil may affect the stress-related HPA axis activation. Waiting for definitive data, for health-protective and ethical concerns, it is advisable both to discourage PDE5i abuse in athletes and adequately monitor during training/competitions all athletes assuming PDE5i for therapeutic purposes.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.
AUTHOR CONTRIBUTIONS


REFERENCES